

## REMARKS

This application, as amended herein, contains claims 1-27, 110, 112 and 114-116, and newly added dependent claims 117 and 118. Claims 28-52, 111 and 113 have been canceled herein.

The Applicant thanks the Examiner for the indication of allowability of claims 3, 5-17, 19, 20 and 26. However, for the reasons set forth below, it is believed that additional claims are also directed to patentable subject matter.

Claims 1, 2, 4, 18, 21-25, 27, 110, 112, 114-116 were rejected as obvious over Hastings in view of Wang et al. in view of Axelsson. The rejection is respectfully traversed.

Claim 1 is directed to a method for obtaining at least one calibration filter for a mass spectrometry instrument system, comprising the steps of obtaining, for a given calibration ion with its isotopes, measured isotope peak cluster data in a mass spectral range; calculating, for the given calibration ion with its isotopes, relative isotope abundances and actual mass locations of isotopes corresponding thereto; specifying mass spectral target peak shape functions; performing convolution operations between the calculated relative isotope abundances and the mass spectral target peak shape functions to form calculated isotope peak cluster data; and performing a deconvolution operation between the measured isotope peak cluster data and the calculated isotope peak cluster data after the convolution operations to obtain the at least one calibration filter. It is respectfully submitted that the combination of Hastings, Wang et al. and Axelsson do not teach or suggest Applicant's invention, as set forth in claim 1.

Hastings deals with filtering of chromatograms whereas Applicant's invention, as set forth in claim 1, deals exclusively with digital filters for mass spectrums. A chromatogram is a data trace of intensities at a given m/z value as a function of retention time, called a mass chromatogram (Col 4 line 10-11, Col 5 lines 61-63). Hastings deals with digital nonlinear median filter (Col 4 line 22-23 & Col 5 line 59-67), claimed to perform better than a conventional linear filter (Col 4 lines 15-17 & Col 5 lines 59-67).

Hastings' filter is created without the use of any standard ions and without any reference to m/z values. Even if Hastings' filter is applied to a mass spectrum, without the use of any standard ions, Hastings' filter is not a calibration filter and does not calibrate m/z. A mass spectrum is a data trace of intensities at one given retention time as a function of m/z, e.g., Fig. 6A in the present application, and not over different retention times, as in Hastings.

The filter in the present application is a digital filter applied to the mass spectrum, not mass chromatogram, and is linear by construction, see, e.g., Fig. 12. Further, the filter in the present application is created with the use of standard ions and is therefore a calibration filter that calibrate the m/z positions of a mass spectrum. A search through the text of Hastings did not reveal or mention the word "calibration", "standard ion", or "isotope".

The cited portion of Hastings (Col 5 lines 27-35) refers to noise associated with ion generation, selection and detection but does not refers to or even imply the use of calibration ion, let alone its isotopes. A text search throughout the Hastings patent does not reveal "isotope abundances", let alone its calculation.

Hastings, at Col 5 lines 27-35 discusses various sources of noises in a signal measurement process. In particular, these noises and their distributions are not very well understood (Col 5 line 37-39), pointing away from the exact process of isotope abundance calculation at the core of the current application, as set forth in claim 1.

While Axelsson teaches measured isotope peak cluster, it teaches the use of an assumed model molecule (Col 3 lines 31-34 & Col 4 lines 5-8) and an assumed peak shape (Col 3 line 40 and Col 5 line 51). This teaches away from the exact corresponding elemental composition of a standard ion (Applicant's Figs. 7C and 7D) and the calculation of actual peak shape function, as set forth in claim 1. In addition, Axelsson teaches a method for mass determination, not a method of mass spectral calibration. A full text search shows

that Axelsson does not even mention the word "calibration" or "standard ion" used for calibration.

In summary, there is no teaching, suggestion or motivation to combine Hastings, which deals with the very different problems of chromatography, with Wang et al. which deals with optical spectra, where there are no isotopes to be measured (and just mentions mass spectrometry in passing at the end of the specification), with the teachings of Axelsson. However, if merely for argument, Hastings did deal with mass spectra instead of chromatograms, and there existed some rationale (which there is not) for combining Hastings and Axelsson, this combination would not be for the mass spectral calibration through the use of standard ions with exact elemental compositions, an important objective in the present application. Further, Wang et al. does not deal with ions or their isotopes. A full text search reveals no use of "ion" or "isotope" throughout Wang et al. Even if Hastings, Axelsson, and Wang could conceivably be combined, the use of standard ions with exact elemental composition for the creation of mass spectral calibration filter would still be outside of the conceived combination. Thus, it is submitted that the rejection of claim 1 should be withdrawn, and that claim 1 should be allowed.

Independent claim 22 is directed to a method of processing raw mass spectral data, comprising the steps of applying a total filtering matrix to the raw mass spectral data to obtain calibrated mass spectral data, wherein the total filtering matrix is formed by: measured isotope peak cluster data, obtained for a given calibration ion in a mass spectral range relative isotope abundances and actual mass locations of isotopes corresponding thereto, calculated for a same calibration ion, specified mass spectral target peak shape functions, convolution operations performed between the calculated relative isotope abundances and the mass spectral target peak shape functions to form calculated isotope peak cluster data; and a deconvolution operation performed between the measured isotope peak cluster data and calculated isotope peak cluster data after the convolution operations to obtain at least one calibration filter for the total filtering matrix. Thus, claim 22 is similar to claim 1, but uses the filter to process raw spectral data. For

the reasons set forth above with respect to claim 1, it is submitted that claim 22 is also patentable.

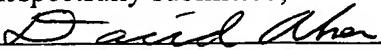
Newly added claims 117 and 118, which depend from claim 22 and claim 1, respectively, state that that the calibration filter is a linear filter based on convolutions (Equations 2 & 3 in Applicant's specification) or matrix operations (Figure 12 in Applicant's specification) or other mathematically equivalent operations such as Fourier transform, and a digital filter applied to the mass spectral data after its acquisition (Equations 2 and 3 and Figure 12), respectively. These claims serve to further distinguish from Hastings. For example, because Hastings is directed to chromatograms, a non-linear filter is taught in Hastings. There would be no reason to use the non-linear filter of Hastings in the mass spectrometry method of the present invention. Thus, it is submitted that claims 117 and 118 are also directed to patentable subject matter.

The remaining claims that have been rejected depend from either claim 1 or claim 22. These claims recite further limitations, which in combination with the limitations of either claim 1 or claim 22, are not shown or suggested in the art of record. For the reasons set forth above with respect to claim 1, it is submitted that these claims are also directed to patentable subject matter.

It is respectfully submitted that this application is in a condition for allowance. However, if there are any issues that remain, the Applicant respectfully requests that the Examiner telephone the undersigned with a view toward resolving those issues.

A check in the amount of \$735 is enclosed (\$525 for a three-month extension of time, \$185 and for presentation of a multiple dependent claim, and \$25 for one additional claim (27 claims canceled and 28 claims added)). It is believed that no additional fee is due with this paper. However for additional required fees, charge deposit account no. 502244.

Respectfully submitted,

  
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02 FC:2616 185.00 OP  
03 FC:2253 525.00 OP